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Review

Pharmaceutical prospects of naturally occurring quinazolinone and its derivatives

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ABSTRACT

Quinazolinones belong to a family of heterocyclic nitrogen compounds that have attracted increasing interest because of their broad spectrum of biological functions. This review describes three types of natural quinazolinones and their synthesized derivatives and summarizes their various pharmacological activities, including antifungal, anti-tumor, anti-malaria, anticonvulsant, anti-microbial, anti-inflammatory and antihyperlipidemic activities. In addition, structure-activity relationships of quinazolinone derivatives are also reviewed.

1. Introduction

Quinazolinones, are N-containing heterocyclic compounds that are widely distributed in plants and microorganisms [1]. The quinazolinone nucleus has attracted much interest because of a wide range of pharmacological activities [2]. As therapeutics, many of them display antitumor [3–5], anti-inflammatory [6], antihypertensive [7], antimicrobial [8], anticonvulsant [9] and antifungal activities [1]. It has been reported that different substituents at the 2/3 position of the quinazolinone nucleus markedly influence pharmacological activity [10]. Quinazolinones can be roughly categorized into four groups, including 2-substituted quinazolinone, 3-substituted quinazolinone, 2,3-disubstituted quinazolinone and quinazolinone derivatives. Naturally occurring quinazolinone alkaloids possess a large number of activities. The 2-substituted quinazolinones have antifungal [1] and antihyperlipidemic activities. The 3-substituted quinazolinones possess anti-malaria activity. The 2,3-disubstituted quinazolinones possess anticancer [11], anticonvulsant [12], anti-microbial [13] and anti-inflammatory activities [14].

Natural products with proven utility as significant sources of novel compounds have provided medicinal chemists with an important source of bioactive molecules for developing therapeutic drugs [15–17]. Natural products, from plants and microbes used as traditional folk medicines, remain one of the most significant sources of biologically active compounds [18]. Therefore, drug discovery from traditional folk medicines is important for various human diseases. This review summarizes the pharmacological activities and rational biogenesis pathway of natural quinazolinones. This review summarizes the pharmacological activities and rational biogenesis pathway of natural quinazolinones. Naturally occurring quinazolinones exist in the plants and microorganisms, while quinazolinone derivatives are synthesized by chemist through some chemical reactions in vitro. In this review, apart from natural quinazolinones, we also review quinazolinone derivatives and their structure-activity relationships.

2. Structures

Quinazolinone alkaloids form the basic core of febrifugine(23) and isofebrifugine(22), which have high antimalarial activity and are extracted from the traditional Chinese medicine Dichroae Radix. They have been used as antimalarial drugs for more than two thousand years in China. In the 1940s, the Chinese phytochemist Yongfeng Fu, the drugologists Shaochang Zhang and Xiacheng Zhao and others first

Abbreviations: LDL-C, low-density lipoprotein cholesterol; ACAT, acyl coenzymeA-cholesterol acyltransferase; VLDL, very low-density lipoprotein; EPRS, glutamyl-prolyl-trnasynthetase; PRS, prolyl-tRNA synthetase; *Pfc*PRS, cytoplasmic prolyl-tRNAsynthetase; CAN, cerium (IV) ammonium nitrate; $GABA_A$Rs, GABA type A receptors; GABA, γ-aminobutyric acid; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; AA, arachidonic acid; NSAIDs, nonsteroidal anti-inflammatory drugs; LTs, leukotrienes; 5-LO, 5-lipoxygenase; (cPL), cytosolic phospholipase; QC, quinazolinone-chalcone; PARP, poly-ADP-ribose polymerase; EAC, Ehrlich ascites carcinoma; ET, Ehrlich tumor

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studied the traditional Chinese medicine Dichroae Radix and carried out the first separations of the active antimalarial ingredients febrifugine(23) and isofebrifugine(22) [19]. Koepfli et al. [20] carried out the separations and in 1950 proposed the febrifugine and isofebrifugine skeleton structures for the first time. Quinazolinones are a vital class of fused heterocyclic alkaloids due to their important biological activities.

In natural product research, compounds are isolated from various complex biological matrices (e.g., metabolites from plants, marine organisms, or microbes). The inherent chemical diversity of natural products and derivatives has resulted in a key role for these metabolites and their derivatives in modern drug discovery. In plants, indolquinazolinones are mainly found in *Polygonum tinctorium* Lour., *Strobilanthes cusia*, *Isatistinctoria* and other blue dye-producing plants. Meanwhile, it is also isolated from *Calanthe*, *Couroupota*, *Strobilanthus* and *Wrightia*. Pyrrolquinazolinones, which are mostly vasicinone and deoxyvasicinone derivatives [21], are found in the families of Zygophyllaceae (*Peganum harmala* L., *Nitraria*), Acanthaceae (*Adhatoda*), Malvaceae (*Sida* L.), Crassulaceae (*Sedum*), Papilionaceae (*Galega* L.) and Scrophulariaceae (*Linaria*). In microorganisms, quinazolinones are isolated from *Fusariumlateritium* Nees, the marine bacterium *Bacillus cereus* 041381, the marine sediment-derived fungus *Penicillium paneum* SD-44,*Salicornia herbacea Salcoli6*, the entomopathogenic fungus *Isaria farinosa*, *Streptomyces* sp., *Chaetomium* sp.IFB-E015, *Aspergillus* sp., *Aspergillus nidulans* MA-143, the sea fan-derived fungus *Neosartorya siamensis*, and *Penicillium aurantiogriseum*.

Depending on the position of the keto group, they can be classified into three types. Among the 2(1*H*)-quinazolinones, 4(3*H*)-quinazolinones and 2,4(1*H*,3*H*)-quinazolinediones, 4(3*H*)- quinazolinones are most the prevalent and significant in medicinal chemistry possessing a multitude of pharmacological actions [22]. Natural quinazolinones are mostly biosynthesized from anthranilic acid and tryptophan [21]. For example, fumiquinazoline F(**117**) originates from a fungal nonribosomal peptide synthetase(TqaA). By systematically inactivating every biosynthetic gene in the cluster, followed by isolation and characterization of the intermediates, the biosynthetic sequence of the pathway could be found by Xue Gao. Fumiquinazoline F(117) is biosynthesized from L-tryptophan, L-alanine and anthranilic acid under TaqA [23]. Rutaecarpine (**92**) is biosynthesized from anthranilic acid and L-serine, and anthranilic acid derives from Shikimic acid. Asperlicin (**154**) is constructed from tryptophan, two anthranilate moieties and leucine. Asperlicin C (**156**), produced in the same fermentation, lacked the leucine moiety [24]. Tryptanthrin (**80**) is biosynthesized from anthranilic acid. Oxidative employing either substituted tryptophans and anthranilic acid or tryptophan and substituted anthranilic acids [25]. 3-substituted quinazolinone such as chaetomine, is constructed from anthranilic acid, L-alanine and formic acid. Furthermore, the biogenesis of natural quinazolinones is showed in Fig. 2. Quinazolinone can be roughly categorized into three types, namely, 2-substituted quinazolinones, 3-substituted quinazolinones, 2,3-disubstituted quinazolinones and quinazolinone derivatives [26]. All of these 157 compounds are displayed in Table 1, Fig. 1.

2.1. 2-Substituted quinazolinones

These are mostly derived from microorganisms and seldom from plants. Their substituents are located at C-2 and include long chain alkyl, methyl, hydroxyl, acetyl, amino, indole and aromatic groups; therefore, they have a variety of activities. Quinazolinones from the marine bacterium *Bacillus cereus* 041381 exhibited moderate antifungal activity against *Candida albicans* [75]. Bouchardatine(8), a 2-substituted alkaloid isolated from *Bouchardatia neurococca* (Rutaceae), shows a large number of biological activities including anti-cancer, anti-inflammatory, and anti-tuberculosis effects [76]. Apart from natural products, raltitrexed(17), a synthetic 2-substituted quinazolinone, has been used widely for the first-line treatment of advanced colorectal cancer [77].

2.2. 3-Substituted quinazolinones

Microorganisms in marine environments have been widely recognized as sources of active and characteristic structure secondary metabolites. These types of compounds carry a number of substitutions on quinazolinone, and these substituents are located at C-3. 3-Substituted quinazolinones mainly come from the fungus *Aspergillus* sp., which is collected from submerged decaying wood in marine habitats. Furthermore, fumiquinazoline S is a new compound of the fumiquinazoline class of alkaloids, which has been reported in a number of strains of the marine fungi *Scopulariopsis*, *Aspergillus* and *Acremonium* [78].

2.3. 2,3-Disubstituted quinazolinones

These types of quinazolinones carry substitutions at C-2 and C-3. They have various fused heterocyclic moieties, such as pyrrole, indole, pyridine, piperazine and diazepine. Pyrrolequinazolinones (deoyvasicinone (68), vasicinone(69), luotonin A(77), etc.) are mostly isolated from *Adhatodavasica, Peganum* and *Phaius mishmensis*. These kinds of alkaloids have significant anti-inflammatory, antibacterial and antidepressant activity. Indolequinazolinone alkaloids are the primary active constituents of *Isatis indigotica* Fort. (Cruciferae) whose dried roots and leaves, named “ban lan gen” and “da qing ye”, respectively, in Chinese, are used in traditional Chinese medicine for the treatment of various diseases, especially colds, infections, influenza and fever. Furthermore, indolequinazolinone alkaloids reveal antiviral activity [79]. The orchid *Phaius mishmensis* was reported to be a rich source of indolequinazolinone derivatives [80]. Pyridinequinazolinones are mainly rutaecarpine analogs from *Evodia rutaecarpa*, which are commonly used as an anti-inflammatory drug in traditional Chinese medicine [81].

2.4. Quinazolinone derivatives

This group of compounds contains further modifications of the A- and B-rings and includes newly and previously synthesized analogs. The substituents of 2-substituted quinazolinone derivatives are commonly 3-methoxyphenyl, 2-hydroxyphenyl, cyano, amino and methyl moieties. 3-substituted quinazlinone derivatives are substituted by nitrogen heterocyclic ring such as tetrazolyl. 2,3-disubstituted quinazolinone derivatives are substituted by alkyl, furan-2-yl, halogen, amide and arene derivatives. Among these kinds of substitutions, furan-2-yl is the most common. This type of substitution can be beneficial to enhance their bioactivity. Some quinazolinone derivatives can be further modified to augment their potential and reduce side effects. These promising results encouraged us to continue to pursue the modification of quinazolinone.

3. Pharmacological activities and corresponding structure-activity relationships

Quinazolinones and their derivatives constitute an important class of heterocyclic compounds occupying an important position in medicinal chemistry. Natural quinazolinones have been showed to exhibit various pharmacological activities, which primarily include anticancer [82], anti-inflammatory [83], antifungal [84], antihyperlipidemic, anticonvulsant [85], antimalarial [86] and antimicrobial activities. The naturally occurring quinazolinones are medicinally and pharmaceutically important owing to their various biological activities [87,88]. A number of drugs have been developed from natural sources with natural compounds being a major source of drug candidates. Apart from natural products, many quinazolinone derivatives possess pharmacological activities following the modification of their structures, and these may provide an important scaffold for designing new bioactive anticancer agents. 2,3-Disubstituted quinazolin-4(3*H*)-one has good antitumor activity [89]. Structural modification studies are in progress to